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| 09/610,313 | 07/05/2000 | Susan Barnett | PP01631.101 | 4221 |

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| EXAMINER | |
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| WHITEMAN, BRIAN A | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/610,313 | Applicant(s) BARNETT ET AL. | |
|---|---|---|---|
| | Examiner Brian Whiteman | Art Unit 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-40 and 42-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *48 and 49* is/are allowed.

6)☒ Claim(s) *1-40,42-47,50 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *12/27/02* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### Non-Final Rejection

Claims 1-40 and 42-51 are pending.

Applicants' traversal, the cancellation of claim 41, the amendment to claims 1, 36, and 49 in paper nos. 15 and 21 is acknowledged and considered. Paper no. 21 is a duplicate of paper no. 15.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/27/02 has been entered.

### *Information Disclosure Statement*

Applicants are required to correct the Patent No. for the document A2 because the document does not have a proper US Patent No (RE 33,653).

The other U.S. Patents cited on the IDS in paper no. 19 were considered and initialed on the 1449 by the examiner. However, if the application was allowed the U.S. patents would not be printed on the patent. If the applicants want the US Patents to be printed should the application be allowed, the applicants should submit a 1449 listing the class/subclass for each US Patent listed on the 1449.

### *Specification*

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (e.g., pages 20 and 32). Applicant is required to delete any embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-40 and 41-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-40 and 41-47 as best understood, are readable on a genus of a polynucleotide sequence encoding a polypeptide including an antigenic HIV Pol polypeptide, wherein the polynucleotide sequence encoding said Pol polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 30, 31, or 32, wherein the genus of polynucleotide sequences is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates production of a genus of a polynucleotide sequence encoding a polypeptide including an antigenic HIV Pol polypeptide, wherein the polynucleotide sequence encoding said Pol polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 30, 31, or 32. The as-filed specification provides sufficient description of an antigenic HIV Pol polypeptide set forth in SEQ ID NO: 30, 31, or 32. Furthermore, the as-filed specification that the synthetic HIV Pol polynucleotides will be capable of higher protein production compared to wild-type HIV Pol polynucleotide sequences (page 36). The specification and the art of record teach that HIV pol comprises the enzymes reverse transcriptase (RT) and integrase (INT). The claims recite a structure (polynucleotide encoding an antigenic HIV Pol polypeptide), but do not recite a function for the genus of polynucleotide sequences. In addition, in view of the phrase "HIV Pol polypeptide", the polypeptide has to be identical to one found in an HIV in nature. The specification does not disclose how to distinguish between natural amino acid sequence and non-natural sequence that is also at least 90% identical. One skilled can envision a sequence that is at least 90% identical to the claims SEQ ID NOs., but would be unable to determine if it was an HIV sequence that was found in nature. Thus, in view of the reasons set forth above and the numerous and the involves contained in an HIV Pol polypeptides, the specification does not disclose which activities correspond to the claimed genus of polynucleotides with 90% sequence identity to the claimed SEQ ID NOs or how to distinguish between natural amino acid sequence and non-natural sequence that is also 90% identical.

It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of polynucleotide sequences as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of polynucleotide sequences that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of a polynucleotide sequence encoding a polypeptide including an antigenic HIV Pol polypeptide, wherein the polynucleotide sequence encoding said Pol polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 30, 31, or 32. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of polynucleotide sequences that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells

Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of a polynucleotide sequence encoding a polypeptide including an antigenic HIV Pol polypeptide, wherein the polynucleotide sequence encoding said Pol polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 30, 31, or 32 that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Applicant's arguments filed 12/27/02 have been fully considered but they are not persuasive because they are not applicable to the new 112 written description rejection.

Claims 1-40, 42-47 and 50-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an expression cassette comprising the polynucleotide sequence set forth in SEQ ID NOs: 30, 31, or 32 and a method of generating an immune response comprising administering to a subject a gene delivery vector comprising the expression cassette comprising the polynucleotide sequence operably linked to a promoter, does not reasonably provide enablement for a polynucleotide sequence encoding a polypeptide including an antigenic HIV Pol polypeptide, wherein the polynucleotide sequence encoding said Pol polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 30, 31, or 32 and using a composition comprising the

nucleotide sequence in a method of immunization in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of a polynucleotide sequence encoding a polypeptide including an antigenic HIV Pol polypeptide, wherein the polynucleotide sequence encoding said Pol polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 30, 31, or 32, particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g. used in an expression cassette for generating an immune response in a mammal.

The invention lies in the field of producing a composition comprising an expression cassette comprising an HIV Pol polypeptide set forth in SEQ ID NOs: 30-32 and using the composition for immunizing or generating an immune response in a subject.

Furthermore, with respect to claims 22-40, 42-46, 50-51 that encompasses a composition or expression cassette for use in generating an immune response comprising a specific nucleotide sequence not operatively linked to a promoter. The specification provides sufficient guidance for one skilled in the art to make and use a gene delivery vector or composition comprising a

polynucleotide operatively linked to a promoter. However, the specification fails to provide sufficient guidance or factual evidence for one skilled in the art to make and use an expression cassette or gene delivery vector, which expresses a nucleic acid sequence comprising a promoter that is not operatively linked to any specific nucleotide sequence in the claimed composition or expression cassette. The teachings in the specification are directed to using a promoter to express the polynucleotide sequence. The as-filed specification provides guidance or evidence for how to make and use vectors comprising a promoter operatively linked to a polynucleotide sequence to direct nucleotide expression, however the claims do not recite such a structural limitation. Thus, to the extent the claims fail to recite distinguishing features to commensurate with the level of guidance presented, the claims are not considered enabled.

The state of the art exemplified by Gurunathan et al. indicates that the goal of developing effective vaccines for a particular disease depends on several factors:

1) Identification of a conserved antigen capable of inducing protection is an outbred population.
2) Design vaccines that can induce an appropriate qualitative and quantitative immune response.
3) Some diseases require different types of immune responses for effective primary and memory immunity (*J Immunol*, Vol. 161(9), pg. 4563, November 1998).

In addition, the state of the art regarding HIV vaccines as exemplified by Nathanson et al. *The Journal of Infectious Disease*, Vol. 182, pp. 579-89, 2000) suggest that the formulation of an effective AIDS vaccine constitutes a daunting challenge for a number of reasons, including the following:

1) the ability of the virus to persist, to replicate in the face of a vigorous immune response and ultimately, to destroy the integrity of the immune system by an attack on CD4 helper T lymphocytes;
2) the question of whether partial immunity will suffice to protect vaccines against eventual disease;

3) the absence of a single clear-cut immune correlate of protection;
4) the difficulty of inducing neutralizing antibodies;
5) the necessity of defining and inducing CTL epitopes that are immunodominant for each of many different MHC class I haplotypes;
6) the question of whether a vaccine formulated on a virus of a single clade will protect against infection with viruses of other clades;
7) the question of whether an effective vaccine must induce mucosal immunity; and
8) the difficulty of developing an attenuated virus strain is immunogenic (page 586).
Furthermore, Nathanson states that 15 years have past since HIV-1 was isolated and yet the possibility of an AIDS vaccine still appears quite remote (page 579).

The application contemplates: 1) Expression assays for the synthetic coding region of Pol, Env, and Gag-protease expression cassettes; 2) In vivo immunogenicity of Gag, Pol, and Env expression cassettes using plasmid DNA carrying the synthetic Gag, Pol, and Env expression cassette; 3) DNA immunization of non-human primates by administering intradermally, mucosally, bilaterally, intramuscularly into the quadriceps using various doses of a synthetic Pol, Env, and Gag-containing plasmid; 4) In vitro expression of recombinant alphavirus vectors or plasmid containing the synthetic Gag, Pol, and Env expression cassette; 5) In vivo immunogenicity of recombinant Sindbis replicon vectors containing Gag, Env, and Pol expression cassettes in mice by using intramuscular and subcutaneous routes.

The disclosure further claims that these experiments will exhibit increased potency for induction of cytotoxic T-lymphocytes (CTL) response and humoral immune response by using the Gag, Pol, and Env expression cassettes.

The as-filed specification provides sufficient guidance for one skilled in the art to make an immunogenic composition comprising an expression cassette comprising of a polynucleotide sequence set forth in SEQ ID NOs: 30-32 and the expression cassette further comprising a viral polypeptide or antigen selected from the group consisting of Gag, Env, vif, vpr, tat, rev, vpu, and

nef. In addition, the as-filed specification provide sufficient guidance for one skilled in the art to use the immunogenic composition comprising an expression cassette comprising of one the polynucleotide sequences set forth in SEQ ID NOs: 30-32 operatively linked to a promoter in a method of producing an immune response in a subject by using a route of administration (e.g. i.m.).

Furthermore with respect to claims 29-40 encompassing a method of immunization of a subject using an immunogenic composition comprising the expression cassette comprising an HIV Pol polypeptide encoded by a polynucleotide sequence that is 90% identical to the polynucleotide sequence set forth in SEQ ID NOs: 30, 31, or 32, the state of the state of the art for immunizing a subject against HIV and in view of the disclosure does not provide sufficient guidance for one skilled in the art to produce a therapeutically effective (partial and/or full protection and treatment) in a subject. The breadth of the term "immunization" encompasses protecting and not protecting a subject from HIV. In view of the state of the art for producing an HIV vaccine and the lack of guidance by the specification for protecting a subject against HIV, the as-filed specification does not provide sufficient guidance for one skilled in the art to use the expression cassettes exhibiting the contemplated biological functions as sought in the disclosure (*e.g.* under conditions that are compatible with expression of said expression cassette) in a method of immunization of a subject. The disclosure does not address what amount of expression of the Pol polypeptide is required in a subject to produce a treatment (encompasses partial/complete protection) and/or prevention (total protection) in said subject. Furthermore, the specification does not provide sufficient guidance for how one skilled in the art would circumvent the immunological response of subject for a sufficient time for the Pol polypeptide to

be expressed at a sufficient amount to produce a therapeutic response in the subject. This is important because the modulation of the expression level is necessary for each polypeptide to elicit a desired immune response without modifying or shutting the down host cell function and causing negative effects similar to those of traditional vaccines (Azevedo et al., *Brazilian Journal of Medical and Biological Research*, Vol. 32, page 152, 1999). In addition, as-filed specification does not address the concern with repeated administration of an immunogenic vector since repeated administration would cause decrease expression of the desired Pol polypeptide. Also, it would take one skilled in the art an undue amount of experimentation to determine how to target a specific tissue, which requires that the gene delivery vector avoids degradation in the blood stream and integrates into the desired targeted tissue or cells.

Furthermore, the examples in the as-filed specification appear to be prophetic examples due to the wording of the each example (*e.g.* verbs are in present tense form). In view of the unpredictability of HIV immunization and the doubts expressed in the art of record, one skilled in the art would not be able to reasonably correlate that the examples set forth in the as-filed specification are working examples. In view of these factors (state of the art for producing an HIV vaccine and the prophetic examples in the specification) and the concerns listed above, it is not apparent to one skilled in the art how to reasonably extrapolate experiments comprising prophetic examples to any method of immunization of a subject comprising an immunogenic composition comprising an expression cassette, comprising a polynucleotide sequence encoding a synthetic HIV Pol polypeptide set forth in SEQ ID NOs: 30-32.

In addition to the doubts expressed by Nathanson, the state of art exemplified by McCluskie et al. (*Molecular Medicine*, 5, pp. 287-300, 1999) teach that "the realization that

results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in non-human primates", that "IM injection of plasmid DNA vaccines, while highly immunogenic in mice...was found only to be relatively so in chimpanzees..., and especially not all in Aotus monkeys"' and that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but note necessarily vice-versa" (page 296, column 2, second and third paragraphs). In addition, McCluskie et al. teach that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predicative they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological reponses to the antigen" (page 297, column 1).

Thus, it is not apparent as how one skilled in the art reasonably extrapolates, without undue experimentation, from the scope of prophetic examples to the full scope of the claimed invention that would generate a treatment (immunization) in any subject against any subtype of HIV. Even if the specification contemplated that a clear improvement using the synthetic expression cassettes in an immunogenic composition has been prophetically displayed in mice, it is not apparent as to how the prophetic examples are reasonably extrapolated to the full scope of the claimed invention, encompassing any subject (*e.g.*, snake, bird, fish, mammal, etc.) particularly given that there is no vaccine generation evidence showing that the prophetic examples are a general phenomenon, and given the doubts expressed in the art of record.

With respect to vaccination methods encompassing routes of administration, e.g., intranasally and intramuscular, the state of the art exemplified by McCluskie teaches that the route of delivery of the DNA vaccine can have an impact on the

efficiency of transfection as well as the types and location of cells transfected, and thus potentially on the nature of the immune response (pg. 295). In addition, McCluskie teaches that many different routes have been shown to be effective for DNA delivery in mice; however, few studies have compared responses obtained with different routes using the same antigen-expressing DNA, dose, and immunization schedule. There have been even fewer studies to compare routes of administration in non-human primates (pg. 295).

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable making and using an expression cassette comprising the polynucleotide sequence set forth in SEQ ID NOs: 30, 31, or 32, does not reasonably provide enablement for a polynucleotide sequence encoding a polypeptide including an antigenic HIV Pol polypeptide, wherein the polynucleotide sequence encoding said Pol polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO: 30, 31, or 32. One would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the In Re Wands Factors including the lack of guidance in the application's disclosure, the unpredictability of producing nucleotide sequences encoding a HIV Pol polypeptide with 90% sequence identity to the claimed SEQ ID NOs. In addition, the prophetic examples as provided in the specification do not reasonably extrapolate to the full scope of the claimed invention.

Applicant's arguments filed 12/27/02 have been fully considered but they are not persuasive but they are not persuasive because they have not provided any new grounds to overcome the rejection set forth above. Thus, it is readily apparent that the as-filed specification fails to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement, e.g. Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997).

Furthermore, with respect to the assertion that skilled worker could have easily used the BLAST or any number of similar programs to determine the % identity as between sequences or could have readily generated any sequence falling within the scope of the claims using routine methods.

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.
> In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification and the applicants' traversal (See page 5 of traversal, which states, "the specification details how to determine nucleotide sequence identity and moreover amply describes that the Pol polynucleotide encoded by these

sequences include Pol antigen" provide no more than a plan or invitation in view of the art of record exemplifying the unpredictability of using making the claimed genus of polynucleotide sequences, for those skilled in the art to experiment with polynucleotide sequences having 90% identity to the SEQ ID NOs: 30, 31, or 32 as intended by the as-filed specification at the time the invention was made.

See also Genetech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what protocols are required for making and using a genus of the claimed polynucleotide sequences, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the assertion in the specification to the full breadth of the claimed invention. Therefore, the as-filed specification is not enabled for the claimed invention.

Furthermore, the traversal is not found persuasive with regard to a method of immunization in a subject, because it is not apparent as how one skilled in the art reasonably extrapolates, without undue experimentation, from the scope of generating an immune response to the full scope of the claimed invention that would generate a immunization (encompasses partial/total protection) in any subject against any subtype of HIV. The term "immunization" in claim 29 encompasses protective or not protective (as admitted in applicants' traversal) and the specification does not teach how to protect a subject against an HIV infection. Even if the

specification contemplated that a clear improvement using the synthetic expression cassettes in an immunogenic composition has been prophetically displayed in mice, it is not apparent as to how the prophetic examples are reasonably extrapolated to the full scope of the claimed invention, embracing a method of immunization of a subject (*e.g.*, snake, bird, fish, monkey, human, etc.) particularly given that there is no immunization generation evidence showing that the prophetic examples are a general phenomenon, and given the doubts expressed in the art of record. Therefore, the specification is not enabled for using the claimed expression cassette in a method of immunization of a subject.

***Conclusion***

Claims 48 and 49 are free of the prior and are in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER